EDITORIAL

The Dilemma Between Efficacy as Defined by Regulatory Bodies and Effectiveness in Clinical Practice

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Editorial to accompany the article "New Drugs: Evidence Relating to Their Therapeutic Value After Introduction to the Market" by Mariam Ujeyl et al. in this issue of Deutsches Ärzteblatt International

In order to be launched on the market, drugs must be considered to meet the safety, efficacy, and pharmaceutical quality criteria established in the German Medicines Act. Drugs are evaluated within the framework of a risk/benefit analysis, as it is called in the Act, performed by the licensing authorities on the basis of clinical trial results submitted by the manufacturer. If the risk/benefit analysis is unfavorable, approval may be refused.

From a physician's perspective, however, the availability of data or the best available evidence when a drug is licensed is rather unsatisfactory. This is because the Phase II or III clinical trials conducted before approval are of little use in drawing conclusions on the therapeutic effectiveness of new drugs in ordinary conditions.

This was evidently the reason that led Mariam Ujeyl and her colleagues to evaluate the features of 81 licensing studies of 39 drugs that had been presented to the European drug approval body, the EMA (European Medicines Agency), in 2009 and 2010, in a striking piece of scientific research (1). The results were sobering and should give pause for thought to those who still equate approval with proof of benefit: information on a patient-relevant endpoint was provided for only 46% of approvals, and for only 28% of approvals was it possible to determine whether the new drug was superior to an active control.

From approval to care

How should doctors be enabled to determine the value of a new drug after approval in the face of such licensing quality? In certain fields, such as oncology, this dilemma between efficacy for approval and benefit in patient care has already been discussed many times (2, 3). As a result, in clinical trials of oncology drugs, endpoints that are appropriate to the treatment aim and that reflect benefit to patients must be chosen. Overall survival is usually the endpoint that allows the best conclusions to be drawn, but in some clinical situations, such as the treatment of rare diseases and preliminary treatment of cancers, quality of life and symptom control are more important endpoints than survival.

Endpoints that reflect benefit to patients include the following:

- Reduced mortality and morbidity burden
- Improved quality of life
- Prolonged overall survival
- Remission-free interval.

Frequently used surrogate parameters such as progression-free survival are inaccurate, and a correlation with overall survival can usually not be demonstrated. However, such parameters are found in most presented licensing studies (4, 5).

Licensing studies are not studies of benefit

However, such trials do little to enable physicians to provide patients with suitable explanations of the benefit of a new drug immediately after it has been authorized, or to make a joint decision with patients on therapeutic intervention.

Patient-oriented benefit cannot be deduced on the basis of such licensing studies, particularly when pre-approval clinical trials have not provided a single comparison of patient-oriented outcomes such as data on quality of life with drugs that are already available. Although the absolute efficacy of the drug has been investigated as required by the German Medicines Act, this does not allow determination of its relative efficacy in comparison to other drugs or interventions, or even of how the benefit of the drug compares with that of standard treatment.

Among the reasons for this are the following:

- Clinical trial design (e.g. comparator intervention different from current standard treatment)
- Strict inclusion criteria (e.g. exclusion of elderly patients, patients with comorbidities, and/or those with impaired kidney or liver function)
- Selection of endpoints that are not patient-relevant
- Research usually lasting only a few weeks to months, with insufficient follow-up data, or frequently none at all.

Because of this, efficacy is often overestimated and risk underestimated, because study populations are too small to identify rare adverse reactions reliably: At least 3000 patients must be enrolled in a trial to identify a risk of 1:1000, and at least 30 000 to identify a risk of 1:10 000. The endpoints accepted for approval are also problematic: For example, in oncology the response

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rate or time to progression do not make it possible to draw reliable conclusions on improved patient-oriented benefit and, therefore, reduced mortality and disease burden and improved quality of life in particular (see also section 35b of the German Social Code (SGB, *Sozialgesetzbuch*), Part V).

Research needed after approval

Both benefit evaluation and risk evaluation are incomplete on approval: They last for as long as a drug is available. During the phase of uncertainty after approval, health services research should therefore be conducted for two to three years. This research must be able to answer questions on patient-oriented benefit and fairness of allocation, using appropriate methods as part of good-quality trials (7).

It is important not to make the mistake of thinking that section 25.5 of the German Medicines Act, which states that an unfavorable risk/benefit ratio is grounds for refusal of approval, refers to patient-oriented benefit. The knowledge available when approval is granted simply does not allow a benefit for patient groups not selected for age, sex, or concomitant diseases, as treated in ordinary clinical conditions in hospitals or private practices, to be deduced from licensing studies characterized by inclusion and exclusion criteria. These circumstances are more than confirmed by the helpful analyses in the publication by Mariam Ujeyl et al. and are supported by the facts.

These considerations doubtless also have implications for current evaluation procedures in accordance with Germany's Pharmaceutical Market Restructuring Act for Statutory Health Insurance (AMNOG, *Arzneimittelmarktneuordnungsgesetz*). In many cases, the required early assessment can only take the form of a preliminary assessment of relative benefit and additional benefit in comparison to other drugs and measures. Germany's Federal Joint Committee (G-BA, *Gemeinsamer Bundesausschuss*) will therefore often be obliged to demand subsequent additional studies, particularly for oncology drugs, in order to arrive at an evaluation that has been verified and is as conclusive as possible following subsequent assessment two to three years later, for example. This evaluation should also ultimately be the basis of price negotiations. Trials from health services research could be of great use here.

The requirements stated in AMNOG could help to increase the proportion of good-quality trials that can form the basis of reliable conclusions, in order to make early assessment of benefit a positive procedure. This would certainly present a significant benefit of the new legal stipulations.

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